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06/816,838	01/07/86	FERNANDO F	

CUSHMAN, DARBY AND CUSHMAN
1615 L STREET, N.W.,
WASHINGTON, DC 20036

EXAMINER	
WADDELL, F	
ART UNIT	**PAPER NUMBER**
125	7

DATE MAILED: 02/04/87

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-7 & 10-12 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-7 & 10-12 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.
8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).
10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.
12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. 112, first paragraph, as containing insuffient exemplary matter to support items (1) and items 2 B-G and item 2I.

Claims 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the above objection to the specification. Note that "greater than about 2" in item 1 and "about" in the other items broadens the original disclosure.

Claims 11 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite for failing to recite the specific tests used to measure antithrombotic and anti-coagulent activity. The numeric values for different tests may vary. It appears that different values for the ratio will result depending on whether KCTT, ACTT, Yin's or anti-Xa are used in determining the ratio.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless-
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 to 7 and 10 to 12 are rejected under 35 U.S.C. 102 (b) as being anticipated by Thrombosis Research-S.

1976 only

The low molecular weight heparin fractions disclosed in the Thrombosis Research publication appear to fall within the upper range of the claims.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1 to 7 and 10-12 are rejected under 35 U.S.C. 103 as being unpatentable over the British patent and Hladovec, et al in view of Nader et al, Waldman et al and Thrombosis. The prior art teaches the sulfation of heparin fractions to produce materials with anti-coagulation properties. See the decisions in Serial Nos. 931,293 and 347,026.

The remarks in the parent case regarding the structures of the polysaccharides of the Experienta reference being different from the structures of the polysaccharides herein do not obviate the rejection since the sulfation of polysaccharides for the purpose of the instant invention is clearly suggested by the reference and because the prima facie case of obviousness has not been properly rebutted with unexpected results.

The remarks and Declaration in the parent case directed to the disclosure of the British patent do not overcome the rejection since the reference suggests sulfating materials obtained from the mother liquid of a heparin purification process, which materials are

employed in the instant invention (see specification, page 4, lines 13-23). The remarks regarding depolymerized heparin do not obviate the rejection since (1) all claims do not call for depolymerized heparin, (2) it is old to depolymerize heparin and (3) such units are deemed present in the mother liquids of the British patent, which suggests sulfating the same.

The remarks in the parent case that the "only way to increase the ratio is by the depolymerization process of the present invention..." are not well taken since (1) the claims do not call for a critical depolymerization step, (2) the depolymerization of heparin is old and (3) to sulfate the resulting polysaccharide with expectation of a product with heparin-like activity is clearly suggested by the references.

The remarks regarding an improved "ratio" do not obviate the rejection since (1) the claims are not drawn to processes of improving the ratio and (2) because page 4 (lines 8 to 10) of the instant specification teaches the additional activity to be an asset in certain instances.

The additional remarks in the Declaration in the parent case regarding the Examples of the British patent being inoperative are not convincing since sulfated products were apparently prepared by the British patentee.

The British patent specification is presumptively operative. The fact that it is possible to work within the scope of the British disclosure and not obtain an operative result is not sufficient. There must also be a showing that one having ordinary skill in the art, making the adaptations such a person would make, could not succeed. In re Lamberti, 192 USPQ 278, 281; In re Michalek, 74 USPQ 107.

The remarks in the parent case regarding the Hladovec reference not relating to heparin fractions have been noted. The reference is still deemed relevant since it teaches heparin-like activity for various sulfated materials, including a depolymerized carbohydrate. Hence, the artisan would expect the sulfation of the depolymerized carbohydrates (heparin fractions) to exhibit heparin-like activity.

The remarks in the parent case regarding optical rotation of the product instantly claimed do not obviate the rejection since the rejection is under 35 USC 103 and various optical activities are expected in view of the numerous optical activities found in the reference.

One skilled in the art, having the benefit of the cited prior art, would have concluded that sulfation of various materials including known heparin fractions such as used in the instant invention would produce materials having enhanced heparin-like properties. The fact that

applicants' sulfated fractions are somewhat different from those used in the British patent does not serve to overcome the rejection. Even though the materials and process recited in the instant claims are not anticipated by the art of record, they are clearly suggested by the disclosures thereof. Applicants' Examples demonstrate only that which would have been expected, i.e. enhanced anti-coagulant actiity after sulfation. While the references do not indicate the effect of sulfation upon antithrombotic activity, they do teach enhanced anti-coagulant activity. This is sufficient to provide the necessary motivation or suggestion required by 35 USC 103 to the skilled artisan.

Applicants' argument in the parent case that the instant oligomers possess a critical ratio of antithrombotic to anticoagulant activity is noted; however there is no evidence in the instant record to support such assertion. Nowhere in the instant record have applicants' presented any data relative to this ratio for the instant materials. The Fussi declaration in the parent case presents data relative to prior art material but none as to those of the instant invention. The only specific data in the record for the instant materials show increased anti-coagulant activity and the presence of antithrombotic acitivty. There is not indication of the actual level of the antithrombotic activity either before or after sulfation of the instant oligomers.

The secondary references teach the relationship of anticoagulant activity of heparins to molecular weights and the importance of sulfation. See particular the Abstracts of the Thrombosis Research articles; the "Discussion" section of Nader et al and the Waldman et al regarding the importance of sulfation.

Even if the degree of antithrombotic activity and thus the ratio of antithrombotic to anticoagulent activity were unexpected, a conclusion of unobviousness is not precluded. See In re de Montmollin, 145 USPQ 416, 417; In re Crounse, 150 USPQ 554, 557; In re Mod, 161 USPQ 281, 283. One having ordinary skill in the are would reasonably expect the claimed compounds to have anticoagulant properties and the subject matter of the invention as a whole would not be unobvious.

In any event, the increased antithrombotic and decreased anticoagulant activity would have been expected by those working in the art. The Thrombosis Research publication teaches that low molecular weight heparin fractions have a high ratio of anti-Xa to APTT. The former is a measure of antithrombotic activity and the latter is a measure of anticoagulant activity.

FREDERICK E. WADDELL
EXAMINER
GROUP ART UNIT 125

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